Estimated benefits and risks of screening for breast cancer

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A controlled randomized trial of breast cancer screening has been initiated in Canada. This paper presents an analysis of the possible benefit from screening relative to the possible radiation risk from mammography for those women who will be screened in the trial. It shows that with modern low-dose mammography, even when a conservative estimate of possible reduction in mortality due to early detection is applied to the data, the estimated benefit substantially exceeds any possible hazard.

On a entrepris au Canada une étude contrôlée et randomisée du dépistage du cancer du sein. Cette communication présente l'analyse des avantages escomptés du dépistage par rapport aux risques possibles de radiation due à la mammographie pour les femmes qui seront soumises aux épreuves de dépistage au cours de cette étude. Il est démontré qu'avec les appareils modernes de mammographie à faible dose, même en évaluant de façon conservatrice la réduction de la mortalité attribuable à une détection précoce, les bénéfices escomptés dépassent de façon marquée les risques possibles.

Breast cancer is a major cause of premature death in Canadian women: it is the leading form of cancer to cause death in women of any age and is the leading cause of all deaths for those between the ages of 35 and 54.[1] Though the mortality rates for the disease have been relatively stable for a number of decades,[2] in the past few years the incidence has started to rise.[3] These statistics reflect that our understanding of the cause of breast cancer is still limited, and they offer little hope that primary prevention of this condition will become possible in the immediate future.[4] The chances for improvement in survival rates through improvements in treatment also appear to be marginal.

Therefore, considerable attention has been focused on screening programs using mammography and physical examination to detect breast cancer early and thus improve its prognosis. A study conducted in the early 1960s among the members of the Health Insurance Plan of Greater New York[5] showed that having mammography and a physical examination annually for a 4-year period could reduce breast cancer mortality by 40% after 5 years in women aged 50 and older. However, the study failed to show any benefit from using these methods to screen women aged 40 to 49.

From 1972 to 1975, 27 Breast Cancer Detection Demonstration Projects were established in the United States, offering annual screening for 5 years to women aged 35 and over. In 1976 concern was expressed that the risk of radiation-induced, or radiogenic, breast cancer might outweigh the benefit from screening women under the age of 50.[6] Following the report of a review committee[7] that recognized that these projects had no means of ascertaining the benefit, mammographic screening was discontinued for all women under 50 except those with a personal or strong family history of breast cancer. The committee did recommend, however, that a controlled, randomized trial be conducted to ascertain the benefit of a screening program using mammography and a physical examination in women under the age of 50 and to assess the relative contribution of mammography to such a program in older women.

To examine the benefit of mammography and a physical examination in screening for breast cancer in women aged 40 to 49 and the independent effect of mammography in women aged 50 to 59, a controlled randomized trial of screening began in Toronto in January 1980; it will be extended to include another eight Canadian cities.[8] The study is being coordinated by the Epidemiology Unit of the National Cancer Institute of Canada (NCIC), and is being funded by the NCIC, the Canadian Cancer Society and the Department of National Health and Welfare, among other agencies. From 50 000 volunteers aged 40 to 49 a study group of 25 000 women will be randomly selected. This group will receive both physical and mammographic examination of the breasts annually for 5 years. The remaining 25 000 will constitute a control group that will receive an initial physical examination but no further screening other than that available through usual health care facilities. In women between the ages of 50 and 59 screening by physical examination alone

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and screening by physical examination in combination with mammography will be compared; 20 000 women will be randomly selected to receive mammography (the screened group) and another 20 000 will receive a physical examination only (the control group). Both groups will receive yearly examinations for 5 years. All participants in the trial will be taught breast self-examination and will be monitored for breast cancer for at least 15 years.

It is important that participants in clinical trials not be unknowingly exposed to risks that could outweigh any benefits they might receive from their participation. This precept is particularly applicable in the present trial since those who receive mammography will be exposed to radiation, even though at very low doses. The consent form used in Toronto and approved by the University of Toronto's human experimentation committee adequately discusses the risk and potential benefit from participating in the trial. However, it is necessary for the investigators as well as the participants to have a basis for assessing the degree of risk from low-dose radiation. At present this can only be derived by extrapolation from the risk of high-dose radiation (mostly above 100 rad).[9] Using such an extrapolation one can calculate the ratio of possible risk to potential benefit of the program. This paper presents the results of such a risk/benefit analysis relative to the expected mortality of the participants.

Methods

Estimated cancer incidence and mortality

A simple mathematical model was used to estimate the cancer incidence and probable mortality among those who will participate in the trial. It was assumed that a group of women would enter the trial at a certain age, free of clinical symptoms of breast cancer. The appropriate single-year age-specific breast cancer incidence was then applied to the group to obtain the expected number of cases of breast cancer for that year. The appropriate single-year age-specific rate of death from diseases other than breast cancer was then applied to those in whom, theoretically, breast cancer did not develop during that year to find the expected number of deaths from other causes in the group. Those who survived the year and were free of breast cancer were then assumed to proceed to the next year of age, and the same procedures were repeated. The breast cancer incidence and the rate of death from other causes used in this paper are from data on malignant disease in Canada in 1975[10] and on mortality in Canada in 1971.[11]

Those with breast cancer are subjected each year to the appropriate breast cancer mortality and to the competitive mortality from other causes. The breast cancer mortality may be expressed as the probability a woman will die in a given year if she had breast cancer at the start of that year. For this study the following probability values were used: 0.061 for each of the first 5 years after diagnosis, 0.034 for each of the next 5 years and 0.010 for each of the next 10 years. After 20 years it was assumed that the risk of dying from breast cancer among the breast cancer patients was negligible. These values are approximately 25% lower than those reported in the United States by the Surveillance, Epidemiology and End Results Program,[12] as they were adjusted to make the breast cancer incidence rates correctly predict the reported age-specific breast cancer mortality rates in Canada.[10] The apparently lower mortality in Canada could result from an under-reporting of incidence or an over-reporting of mortality in the United States, a genuine difference in Canadian survival rates or a combination of all three.[13] It should be noted that using these higher survival rates in our model underestimated the benefit derived from screening and therefore made our assessment of this benefit more conservative.

Thus, the model may be used to estimate the probable number of breast cancer cases, the number of deaths from breast cancer and the average age at death from all causes for women in the control group, by age at entry to the study. To calculate the corresponding probabilities for those screened by mammography it is necessary to allow for two opposing factors: the benefit from screening and the risk of radiogenic breast cancer.

Screening benefit

The benefit from screening is the reduction in the risk of dying from breast cancer through early detection of the disease. In the study of the Health Insurance Plan of Greater New York breast cancer mortality was reduced by 40% in women aged 50 or more who were screened as compared with those in the same age range in the control group.[5] Though no corresponding decrease in mortality was observed in women under that age, the present trial includes women aged 40 to 49 because improvements in technique have increased the sensitivity of mammography.[7] Now early lesions can be detected in younger women and this may result in a reduction in breast cancer mortality. An objective of the present trial is to ascertain whether such a reduction can now be detected. Therefore, we have chosen to use empirical values for a reduction in breast cancer mortality of 20%, 40% and 60%, values that bracket the observed 40% reduction in mortality in women aged 50 or more in the New York study.

Risk of radiogenic breast cancer

In our trial the mammography technique includes the use of a high-speed, single-emulsion film, vacuum-packed with a rare earth screen. Resolution and contrast are excellent for both the craniocaudal and the lateral or oblique projections. Phantom measurements show that the average mid-breast dose for each exposure is 0.07 rad, so that the estimated total absorbed dose to the tissue of both breasts is 0.7 rad for women who have all five mammograms taken (Dr. M. Yaffe: personal communication, 1980).

There is no direct evidence of the carcinogenic risk to humans of such relatively low doses. The only way of estimating such a risk is to apply a mathematical

model to risks measured at much higher doses and extrapolate to low doses. The main sources of data on radiation-induced breast cancer in humans are the studies of survivors of the atomic bomb explosions in Hiroshima and Nagasaki,[14] of patients who underwent extensive fluoroscopy during treatment of tuberculosis,[15] and of patients treated by radiation for postpartum mastitis.[16] An extensive review of the data from all three studies has been presented by Boice and associates,[9] who proposed four possible mathematical models to fit the observed data: a linear additive model, a linear multiplicative model, a linear additive model with a term for cell killing, and a linear multiplicative model with a term for cell killing. The last two models assume an exponential term in the dose–response relationship corresponding to the killing of cells at high levels of radiation that is not included in the first two. The additive, or absolute risk, models add a constant number of radiogenic breast cancer cases to the cases of breast cancer not caused by radiation, independent of the age at which the breast cancer occurs. The multiplicative, or relative risk, models multiply the risk of nonradiogenic breast cancer by a constant factor. The number of radiogenic breast cancers thus depends upon the nonradiogenic rate and on the age at which the radiogenic cancers occur. We used all four models, with the following factors estimated by Boice and associates:[9] the linear additive model adds 6.6 cases of radiogenic breast cancer per million woman-years per rad, and the linear additive model with a term for cell killing adds 8.7 cases; the linear multiplicative model increases the incidence of nonradiogenic breast cancer by 0.42%/rad, and the linear multiplicative model with a term for cell killing increases this rate by 0.57%/rad. These figures are derived from estimates for women exposed to radiation between the ages of 20 and 44 years; there is some evidence that the risk may decrease with increasing age at exposure.[9] Thus, our estimates may again be conservative, leading to a higher estimate of the number of radiogenic breast cancers than will actually occur in the screened subjects, who are, on average, 20 years older. We assumed the increased risk would apply 10 years after the first exposure, the expected latent period.[9]

We used two estimates for total dose: 1 and 2.5 rad. Although measured doses have so far indicated that even the lower figure is a high estimate, we have included both, as the second represents a possible absolute maximum. The effect of radiation induction of breast cancer is included in the model by allowing the age-specific breast cancer incidence rates to be increased by the amount appropriate to the radiation model being considered.

Net benefit

The net difference between risk and benefit expected in the screened groups compared with those expected in the control groups has been calculated by means of two measures: the reduction in the number of deaths from breast cancer expected during the first 15 years of the study, and an estimate of the number of years of life saved by screening, calculated by multiplying the number of individuals in the study group by their estimated average age at death and deducting this from the corresponding figure for the control group. Neither measure, as calculated by our models, is subject to two important biases that have to be considered in analysing screening programs either when control groups are not available or when measures other than mortality are used for end-points.

Lead-time bias arises through attempts to estimate years of life saved by calculating the interval between the dates of diagnosis of the disease and death. If the effect of screening is simply earlier diagnosis rather than postponement of death, this method of calculation produces errors. We have computed years of life saved starting with the year of entry into the study and have not used the year in which a particular cancer was diagnosed; therefore, our estimation is not subject to any lead-time bias.

Length bias arises because slow-growing preclinical disease with a favourable prognosis is more likely to be detected at screening than faster growing tumours since the screening process is independent of disease progression. Because we have made an empirical estimate of the reduction in breast cancer mortality in the screened group as a whole and applied this to the expected incidence of nonradiogenic breast cancer, length bias is not a consideration in this model.

We have assumed that all participants would be present for all five annual screenings. In practice, all will attend the first screening, but a certain percentage will fail to attend one or more further screenings. However, we have used an empirical estimate of the reduction in mortality from screening, and this estimate is independent of the number of individuals who drop out of the study during each year. The 40% benefit reported from the New York study was based on the mortality of all individuals invited to participate, though only 65% attended the first screening. Since agreement to participate is obviously a selective procedure, the benefit should be greater in the present study group than in the New York group. In addition, those who fail to attend the second or subsequent screenings will reduce the average radiation exposure among the study group. Because of this possible drop-out during the study the model again overestimates risk to the group studied.

Results

Breast cancer deaths

Table I shows the cumulative number of expected deaths from breast cancer in the control and screened groups in 5-year intervals up to 30 years after entry to the study, assuming a 40% reduction in breast cancer mortality due to screening. The deaths from radiogenic breast cancer do not begin to accumulate until after the 10-year latent period following entry to the study. The number of deaths in the screened group are shown for the models that give the "best" and "worst" estimates of the risk of screening: the additive model with a total dose after five screenings

of 1.0 rad, and the multiplicative model with a term for cell killing and a total dose of 2.5 rad, respectively. Applying the other models and different doses led to intermediate results. As we expected, the benefit from screening is most pronounced during the first 5 years of the study. Nevertheless, there is a further reduction in breast cancer mortality during the 10 to 15 years after the start of the study. Even with the lowest estimate of the reduction in breast cancer mortality, 20%, there is a saving of 14 lives during the 15-year period for the 25 000 women in the screened group aged 40 to 49 at entry. With the most optimistic estimate of the reduction in mortality, 60%, the number of lives saved is 46. Corresponding figures for the 20 000 women aged 50 to 59 at entry are 16 and 53.

Years of life saved

It made very little difference which mathematical model was applied to estimate the number of radiogenic breast cancers in the first 30 years of study (Table I). However, a more appropriate measure of benefit versus risk may be the number of years of life saved during the lifetime of the screened and control groups, as shown in Tables II and III with the three estimates of the reduction in breast cancer mortality due to screening and the four radiation models. Even with minimal benefit and maximum risk (20% reduction in mortality and a multiplicative model with a cell killing term and a total dose of 2.5 rad) there is a net benefit in years of life saved in the screened group as compared with the control group. The estimated numbers of years of life saved in both age groups are even more substantial when the other radiation models and doses and the other reductions in mortality are applied.

Discussion

The estimates presented of benefit from screening are conservative for the reasons we have indicated. Another factor enhancing this conservatism is that the study group is being selected from volunteers. The experience in the New York study suggests that such volunteers may have a higher than normal incidence of breast cancer and therefore should benefit more from screening.[5] Despite the conservative influence of all these factors, the potential net benefit for those who participate in the study is considerable. The mathematical and radiation models used are realistic, and the main uncertainty in the present analysis is in the empirical values assumed for the reduction in breast cancer mortality derived from using low doses of radiation in mammographic screening. It is because of this uncertainty that the trial was initiated, and it is unrealistic to expect prior proof that the benefit exceeds the risk in such a situation. If such proof was available, a trial would neither be necessary nor ethically justifiable.

We have already responded[17] to the claims of Bross[18] that our estimates of risk and benefit are in error. Others,[9] including Dr. J.C. Bailar of the National Cancer Institute in Bethesda, Maryland (unpublished observations, 1980), support our contention, based on present evidence, that the estimates of Bross cannot

Table I—Estimated cumulative number of deaths from breast cancer after study entry for control and screened groups of 45 000 women aged 40 to 59, assuming a 40% reduction in mortality from screening and applying the "best" and "worst" models for radiation risk from mammography

	No. of years after study entry; no. of deaths					
Group and risk model	5	10	15	20	25	30
Control group	61	195	368	553	734	892
Screened group						
Best model: linear additive; total dose 1.0 rad	38	142	304	487	667	825
Worst model: linear multiplicative with term for cell killing; total dose 2.5 rad	38	142	305	490	672	831

Table II—Estimated years of life saved in the screened group over the lifetime of the 25 000 women aged 40 to 49 on study entry

	Reduction in breast cancer mortality; years of life saved		
Total dose of radiation and risk model	20%	40%	60%
None*	432	909	1437
1.0 rad			
Additive	412	889	1417
Additive + cell killing term	405	883	1411
Multiplicative	402	880	1408
Multiplicative + cell killing term	392	870	1397
2.5 rad			
Additive	381	859	1387
Additive + cell killing term	365	843	1371
Multiplicative	359	836	1364
Multiplicative + cell killing term	332	810	1337

*Years of life saved by screening have been calculated without any estimated reduction due to radiogenic breast cancer.

Table III—Estimated years of life saved in the screened group over the lifetime of the 20 000 women aged 50 to 59 on study entry

	Reduction in breast cancer mortality; years of life saved		
Total dose of radiation and risk model	20%	40%	60%
None*	346	726	1145
1.0 rad			
Additive	339	720	1138
Additive + cell killing term	337	717	1136
Multiplicative	335	715	1134
Multiplicative + cell killing term	331	711	1130
2.5 rad			
Additive	329	709	1127
Additive + cell killing term	323	704	1122
Multiplicative	318	699	1117
Multiplicative + cell killing term	308	689	1107

*Years of life saved by screening have been calculated without any estimated reduction due to radiogenic breast cancer.

be used to compute either the expected risk or the expected benefit. The analysis of breast cancer mortality in the Canadian study of cancer following multiple fluoroscopy, initiated by the NCIC Epidemiology Unit in 1973, should soon be completed. However, it seems unlikely that this study, although larger than any other yet published on women exposed to multiple fluoroscopy, will provide unequivocal estimates of response to doses lower than 50 rad. In fact, the only currently available data that support any assumptions that radiation doses below 100 rad induce breast cancer are derived from the series on women aged 10 to 19 exposed to the atomic bomb.[9]

References

1. MILLER AB: Present status of breast cancer screening (E). *Can Med Assoc J* 1977; 117: 845–846
2. *Cancer Patterns in Canada 1931–1974*, bureau of epidemiology, Laboratory Centre for Disease Control, health protection branch, Dept of National Health and Welfare, Ottawa, 1976: 19–23
3. CUTLER SJ, CHRISTINE B, BARCLAY THC: Increasing incidence and decreasing mortality rates for breast cancer. *Cancer* 1971; 28: 1376–1380
4. MILLER AB, BULLBROOK RD: The epidemiology and etiology of breast cancer. *N Engl J Med* 1980; 303: 1246–1248
5. SHAPIRO S: Evidence on screening for breast cancer from a randomized trial. *Cancer* 1977: 39 (suppl 6): 2772–2782
6. BAILAR JC III: Mammography: a contrary view. *Ann Intern Med* 1976; 84: 77–84
7. BEAHRS OH, SHAPIRO S, SMART C: Report of the working group to review the National Cancer Institute–American Cancer Society Breast Cancer Detection Demonstration Projects. *J Natl Cancer Inst* 1979; 62: 639–690
8. MILLER AB: A proposal for a screening programme for breast cancer in Canada. *Ann R Coll Physicians Surg Can* 1978; 11: 299–300
9. BOICE JD JR, LAND CE, SHORE RE, NORMAN JE, TOKUNAGA M: Risk of breast cancer following low-dose radiation exposures. *Radiology* 1979; 131: 589–597
10. *New Primary Sites of Malignant Neoplasms in Canada*, publ 82-207, health division, Statistics Canada, Ottawa, 1978
11. *Mortality Differences in Canada, 1960–1962 and 1970–1972*, publ 84-533, vital statistics section, health division, Statistics Canada, Ottawa, 1976: 157–163
12. AXTELL LM, ASIRE AJ, MYERS MH (eds): *Cancer Patient Survival. Report Number 5, 1976*, DHEW publ no (NIH) 77-992, US Dept of Health, Education, and Welfare, Bethesda, Md, 1976
13. SHERMAN GJ: *Canadian Cancer Incidence — Completeness, Correlation and Ecological Association in Selected Sites, 1969–1973*, PhD thesis, U of Toronto, 1981
14. MCGREGOR DH, LAND CE, CHOI K, TOKUOKA S, LIU PI, WAKABAYASHI T, BEEBE GW: Breast cancer incidence among atomic bomb survivors, Hiroshima and Nagasaki, 1950–69. *J Natl Cancer Inst* 1977; 59: 799–812
15. BOICE JD JR, MONSON RR: Breast cancer in women after repeated fluoroscopic examinations of the chest. Ibid: 823–832
16. SHORE RE, HEMPELMANN LH, KOWALUK E, MANSUR PS, PASTERNACK BS, ALBERT RE, HAUGHIE GE: Breast neoplasms in women treated with x-rays for acute postpartum mastitis. Ibid: 813–822
17. MILLER AB, HOWE GR, MERKENS BJ, SHERMAN GJ: Mammography (C). *Can Med Assoc J* 1980; 123: 95–97
18. BROSS IDJ: Mammography (C). Ibid: 94–95

Multiple endocrine neoplasia, type II: a combined surgical and genetic approach to treatment

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A family with multiple endocrine neoplasia, type II living in southeastern Ontario is described. Twenty individuals are known to have had medullary carcinoma of the thyroid, pheochromocytoma or both, and the diagnosis of multiple endocrine neoplasia, type II is strongly suspected in five other individuals in the earlier generations. In this family the disease seems to be transmitted by an autosomal dominant gene. A screening program set up for the family in 1977 has in 2 years identified four asymptomatic individuals (three with medullary carcinoma of the thyroid and one with this carcinoma and a pheochromocytoma). The family background, clinical picture, treatment and some of the problems of the screening program are described.

On décrit une famille du sud-est de l'Ontario souffrant de néoplasies endocrines multiples, de type II. Vingt sujets atteints d'un cancer médullaire de la thyroïde, d'un phéochromocytome ou des deux ont été identifiés, et un diagnostic de néoplasies endocrines multiples, de type II, est fortement soupçonné chez cinq autres personnes des générations antérieures. Chez cette famille la maladie semble être transmise par un gène autosomique dominant. En 2 ans un programme de dépistage mis sur pied pour cette famille en 1977 a permis d'identifier quatre sujets asymptomatiques (trois atteints d'un cancer médullaire de la thyroïde et un atteint d'un cancer de ce type accompagné d'un phéochromocytome). Les antécédents familiaux, le tableau clinique, le traitement et quelques-uns des problèmes du programme de dépistage sont décrits.

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Multiple endocrine neoplasia, type II, or Sipple syndrome, is an uncommon but well described familial